Amendments to the Claims

This listing of the claims will replace all prior versions, and listings of claims in the application.

Listing of Claims: 6-11, 17-22 and 26

1. (Canceled)

2. (Canceled)

3. (Canceled)

4. (Canceled)

5. (Canceled)

6. (Currently Amended) A method of determining the relative level of *Dihydropyrimidine dehydrogenase* (*DPD*) gene expression in a tissue sample comprising:

   (a) obtaining a tumor sample from a patient;

   (b) isolating mRNA from said tumor sample;

   (c) determining the amount of *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA by amplifying the mRNA using an oligonucleotide primer ~~having the sequence of~~ SEQ ID: 1, or an oligonucleotide primer at least 80% identical therewith and hybridizes to a complement of SEQ ID NO: 1 under stringent conditions; wherein said isolated and purified oligonucleotide is capable of amplifying a portion of the 5' untranslated region and Exon 1 of a *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 2,

   and;

~~an oligonucleotide having the sequence~~ SEQ ID: 2 or an oligonculeotide primer at least 80% identical therewith and hybridizes to a complement of SEQ ID NO: 2 under stringent conditions; wherein said isolated and purified oligonucleotide is capable of amplifying a portion of the 5' untranslated region and Exon 1 of a *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 1;

(d) comparing the amount of *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA from step (c) to an amount of mRNA of an internal control gene.

7. (Original) The method of claim 6, wherein the tumor sample is frozen after being obtained from the patient.

8. (Original) The method of claim 6, wherein the tumor sample is fixed after being obtained from the patient.

9. (Previously amended) The method of claim 8, wherein the tumor sample is embedded in paraffin after being fixed.

10. (Original) The method of claim 8 or 9, wherein the RNA is isolated in the presence of an effective amount of chaotropic agent.

11. (Original) The method of any one of claims 6, 8, or 9, wherein the tumor sample comprises non-tumor tissue and tumor tissue.

12. (Canceled)

13. (Canceled)

14. (Canceled)

15. (Canceled)

16. (Canceled)

17. (Currently Amended) A method of determining the relative level of *Dihydropyrimidine dehydrogenase* (*DPD*) gene expression in a tissue sample comprising;

(a) obtaining a tumor sample from a patient;

(b) isolating mRNA from said tumor sample;

(c) determining the amount of *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA by amplifying the mRNA using an oligonucleotide primer ~~having the sequence of~~ SEQ ID: 7, or an oligonucleotide primer at least 80% identical therewith and hybridizes to a complement of SEQ ID NO: 7 under stringent conditions; wherein said isolated and purified oligonucleotide is capable of amplifying a portion of Exon 6 of a *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 8,

and;

~~an oligonucleotide having the sequence~~ SEQ ID: 8 or an oligonculeotide primer at least 80% identical therewith and hybridizes to a complement of SEQ ID NO: 8 under stringent conditions; wherein said isolated and purified oligonucleotide is capable of amplifying a portion of Exon 6 of a *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 7;

(d) comparing the amount of the mRNA from step (c) to an amount of mRNA of an internal control.

18. (Original) The method of claim 17, wherein the tumor sample is frozen after being obtained from the patient.

19. (Currently amended) The method of claim 17, wherein the ~~a~~ tumor sample is embedded in paraffin after being fixed.

20. (Original) The method of claim 19, wherein the mRNA is isolated in the presence of an effective amount of chaotropic agent.

21. (Original) The method of claim 17, wherein the tissue sample is obtained from a tumor.

22. (Original) The method of claim 20, wherein a tumor sample comprises non-tumor tissue and tumor tissue.

23. (Canceled)

24. (Canceled)

25. (Canceled)

26. (Canceled)

27. (New claim) A method of determining the relative level of *Dihydropyrimidine dehydrogenase* (*DPD*) gene expression in a tissue sample comprising:

(a) obtaining a tumor sample from a patient, wherein said tumor sample is fixed;

(b) isolating mRNA from said tumor sample, wherein said tumor sample is heated to a temperature in the range of about 50 to about 100°C;

(c) determining the amount of *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA by amplifying the mRNA using an oligonucleotide primer SEQ ID: 1, or an oligonucleotide primer at least 80% identical therewith and hybridizes to a complement of SEQ ID NO: 1 under stringent conditions; wherein said isolated and purified oligonucleotide is capable of amplifying a portion of the 5' untranslated region and Exon 1 of a *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 2,

and;

SEQ ID: 2 or an oligonculeotide primer at least 80% identical therewith and hybridizes to a complement of SEQ ID NO: 2 under stringent conditions; wherein said isolated and purified oligonucleotide is capable of amplifying a portion of the 5' untranslated region and Exon 1 of a *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 1;

(d) comparing the amount of *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA from step (c) to an amount of mRNA of an internal control gene.

28. (New claim) A method of determining the relative level of *Dihydropyrimidine dehydrogenase* (*DPD*) gene expression in a tissue sample comprising:

(a) obtaining a tumor sample from a patient, wherein said tumor sample is fixed;

(b) isolating mRNA from said tumor sample, wherein said tumor sample is heated to a temperature in the range of about 50 to about 100°C;

(c) determining the amount of *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA by amplifying the mRNA using an oligonucleotide primer SEQ ID: 7, or an oligonucleotide primer at least 80% identical therewith and hybridizes to a complement of SEQ ID NO: 7 under stringent conditions; wherein said isolated

and purified oligonucleotide is capable of amplifying a portion of Exon 6 of a *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 8,

and;

SEQ ID: 8 or an oligonculeotide primer at least 80% identical therewith and hybridizes to a complement of SEQ ID NO: 8 under stringent conditions; wherein said isolated and purified oligonucleotide is capable of amplifying a portion of the 5' untranslated region and Exon 6 of a *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 7;

(d) comparing the amount of *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA from step (c) to an amount of mRNA of an internal control gene.

29. (New claim) The method of claims 27 or 28, wherein said internal control gene is β-actin.

30. (New claim) The method of claims 27 or 28, wherein the tumor sample is fixed and embedded after being obtained.

31. (New claim) The method of claims 27 or 28, wherein the mRNA is isolated in the presence of an effective amount of chaotropic agent.

32. (New claim) A method for determining the relative level of *Dihydropyrimidine dehydrogenase* (DPD) gene expression in a fixed paraffin embedded tissue sample comprising:

(a) deparaffinizing the tissue sample to obtain a deparaffinized sample;

(b) isolating mRNA from the deparaffinized sample in the presence of an effective

amount of a chaotropic agent by first heating the tissue sample in a solution comprising an effective concentration of a chatropic compound to a temperature in the range of about 75° to about 100° C for a time period of 5 to 120 minutes and recovering said mRNA from said chaotropic solution; and

(c) subjecting the mRNA to amplification using a pair of oligonucleotide primers capable of amplifying a region of the ERCC1 gene, to obtain an amplified sample;

(d) determining the quantity of ERCC1 mRNA relative to the quantity of an internal control gene's mRNA.

33. (New claim) The method of claim 32 wherein, the internal control gene is β-actin.

34. (New claim) A method for determining the relative level of *Dihydropyrimidine dehydrogenase* (DPD) gene expression in a fixed paraffin embedded tissue sample comprising:

(a) deparaffinizing the tissue sample to obtain a deparaffinized sample;

(b) isolating mRNA from the deparaffinized sample by first heating the deparaffinized tissue sample in a solution comprising an effective concentration of a chaotropic agent to a temperature in the range of about 50° to about 100° C and recovering said mRNA from said solution; and

(c) determining the quantity of ERCC1 mRNA relative to the quantity of an internal control gene's mRNA.

35. (New claim) A method for determining a platinum-based chemotherapeutic regimen for treating a tumor in a patient comprising:

(a) obtaining a tissue sample of the tumor and fixing the sample to obtain a fixed tumor sample;

(b) isolating mRNA from the fixed tumor sample, wherein the fixed tumor sample is

heated in the presence of an effective amount of a chaotrophic agent and wherein the heating occurs at a temperature from about 50° to about 100° C;

(c) subjecting the mRNA to amplification using a pair of oligonucleotide primers capable of amplifying a region of the *Dihydropyrimidine dehydrogenase* (DPD) gene to obtain an amplified sample;

(d) determining the amount of amplified DPD mRNA in the amplified sample;

(e) comparing the amount of DPD mRNA from step (d) to an amount of mRNA of an internal control gene; and

(f) determining a platinum-based chemotherapeutic regimen based on the amount of DPD mRNA in the amplified sample and a predetermined threshold level for DPD gene expression.

36. (New claim) The method of claim 35 wherein the pair of oligonucleotide primers consist of the SEQ ID NO:1 or an oligonucleotide primer at least about 80% identical thereto and SEQ ID NO:2 or an oligonucleotide primer at least about 80% identical thereto.

37. (New claim) The method of claim 35 wherein the fixed tumor sample is heated in the presence of an effective amount of a chaotrophic agent and wherein the heating occurs at a temperature from about 75 °C to about 100 °C for a period of about 5 to about 120 minutes.

REMARKS

Claims 6-11, 17-22 and 26 are pending in the subject application. Claims 6 and 17 are amended to more particularly point out and distinctly claim the subject matter the Applicant considers her invention. Support for amended claims may be found throughout the specification but particularly in paragraph 38 on page 15 and originally filed claims 13-16. New claims 27-37 are added. Support for new claims may be found throughout the specification but particularly in paragraphs 34-42 on pages 12-17 and in originally filed claims 13-16. No new matter is raised.

Rejection of claims 6-11, 17-22 and 26 under of 35 U.S.C. §112, First Paragraph - Written Description

All claims stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the claimed invention is not described in such a way that one of ordinary skill in the art would be convinced that the Applicant was in possession of the claimed genus at the time of filing.

A. Background: Written Description Requirement

The written description requirement of § 112, ¶ 1 is set forth as follows:

> The specification shall *contain a written description of the invention*, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

35 U.S.C. § 112, ¶ 1 (1994) (emphasis added). The Federal Circuit has interpreted this paragraph of the statute to contain a "written description" requirement distinct from enablement. *Vas-Cath v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1117 (Fed. Cir. 1991) (recognizing the severability of the "written description" and "enablement" provisions of § 112, ¶ 1). The Federal Circuit has further determined that compliance with the written description requirement is a

question of fact that will "necessarily vary depending on the nature of the invention claimed." *Id.* (citing *In re DiLeone*, 436 F.2d 1404, 1405, 168 USPQ 592, 593 (CCPA 1971)).

Two recent cases from the United States Court of Appeals for the Federal Circuit provide guidance as to the written description requirement as it pertains to biotechnology. Each case will be discussed in turn.

A.1. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997)

The Federal Circuit applied the written description requirement to biological materials in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) (hereinafter *Eli Lilly*). In *Eli Lilly*, the Court held that genetic material that has only been defined by a statement of function or result is not adequately described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. In *Eli Lilly*, the Court further determined that a claim to a microorganism containing a human insulin cDNA was not adequately described by a statement that the invention included human insulin cDNA. *Id.* at 1567, 43 USPQ2d at 1405.[1]

The trial court invalidated the claims at issue on the basis that the specification did not provide adequate written description of the originally filed claims drawn to the genera of vertebrate, mammalian, or human insulin cDNA. The court opined that the inventors could not provide a description of human insulin cDNA because they were not in possession of that DNA.

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[1]Originally filed generic claims 1, 2, 4, 6 and 7 of U.S. Patent No. 4,652,525 (the '525 patent) recited complementary DNA (cDNA) encoding vertebrate or mammalian insulin. Claim 5 more narrowly recited a cDNA encoding human insulin. The specification of the '525 patent disclosed isolated cDNAs encoding preproinsulin (PPI) and proinsulin (PI) derived from rat. As support for claim 5, the specification disclosed the amino acid sequences of the human insulin A and B chains as well as a prophetic example of how one would go about cloning the corresponding claimed human cDNA. Neither the sequence of a rat nor a human insulin encoding cDNA was disclosed. A careful review of the '525 patent reveals that the rat insulin cDNA was isolated on the basis of size and not sequence, i.e. structure. Therefore, no DNA structure was disclosed.

The court further held that the inventors did not sufficiently describe the genera of mammalian or vertebrate cDNAs by disclosing the species of rat cDNA.

The Federal Circuit affirmed the trial court's decision. The court stated:

> The name cDNA is not itself a written description of that cDNA; it conveys no distinguishing information concerning its identity. While the Example provides a process for obtaining human insulin-encoding cDNA there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words it does not describe the cDNA.

Id. The court stated that as opposed to what was provided in the patent at issue, an adequate written description of genetic material "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." *Id.* at 1566, 43 USPQ2d at 1404 (quoting *Fiers v. Revel*, 984 F.2d at 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993)). Accordingly, the court reasoned that the specification of the '525 patent did not indicate to one of ordinary skill in the art that the inventors had possession of the claimed human insulin cDNA.

A.2. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002)

The Federal Circuit, in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002)(hereinafter referred to as *Enzo*), provides some guidance in assessing the requirements of written description requirement with respect to the claiming of a genus of nucleic acid molecules defined on the basis of nucleic acid hybridization. Claims 4 and 6 of U.S. Patent No. 4,900,659 recited specific deposited nucleic acids as well as a genus of nucleic acids that where "discrete nucleotide subsequences thereof," and a further genus of "mutated discrete nucleotide sequences of any of the foregoing inserts [deposited sequences] that are within said hybridization ratio and subsequences thereof. . . ." *Enzo*, 323 F.3d at 961. The court concluded that, "the written description requirement would be met for these claims:

> . . . if the functional characteristic of preferential binding to *N. gonorrhoeae* over *N. meningitidis* were coupled with a disclosed correlation between that

> function and a structure that is sufficiently known or disclosed. We are persuaded by the Guidelines on this point and adopt the PTO's applicable standard for determining compliance with the written description requirement.

Enzo 323 F.3d at 968. In distinguishing *Eli Lilly*, the court indicated that, "[i]t is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement." *Enzo* 323 F.3d at 964. The court thus appreciated the fact that nucleic acid hybridization has intertwined and inseparable functional and structural attributes.

As indicated in the quote, the Federal Circuit adopted the standards set forth in the United States Patent and Trademark Office Guidelines, Synopsis of Application of Written Description Guidelines, available at http://www.uspto.gov/web/patents/guides.htm, *Id.* citing 66 Fed. Reg 1099 (January 5, 2001) ("the Guidelines"). The Guidelines were promulgated to serve as internal training materials relating to the application of the written description requirement to biotechnology. In its Guidelines, the PTO concluded that the written description requirement can be met by:

> show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or **some combination of such characteristics.**

Guidelines, *Id.* citing 66 Fed. Reg. at 1106 (emphasis added).

Specifically, the court adopted the Guidelines with respect to defining the structure of a nucleic acid on the basis of hybridization to a disclosed sequence, and overturned the district court's granting of a motion for summary judgement invalidating claims relating to nucleic acid variants of the deposited nucleic acids that hybridize to a known sequence under stringent conditions and subsequences thereof. *Enzo* 323 F.3d at 964.

At trial, Enzo's expert witness touched on the policy considerations that must be taken into account when assessing compliance with the written description requirement. He argued that, although a large number of species are within the scope of the claimed genus, such "broad

claim scope is necessary to adequately protect Enzo's invention from copyists who could otherwise make a minor change to the sequence and thereby avoid infringement while still exploiting the benefits of Enzo's invention." *Enzo* 323 F.3d at 966.

The court held that the genus claims 4 and 6 were not invalid as a matter of law and ruled that, "[o]n remand, the court should determine whether a person of skill in the art would glean from the written description, including information obtainable from the deposits of the claimed sequences, sub-sequences, mutated variants, and mixtures sufficient to demonstrate possession of the generic scope of the claims." [emphasis added] *Id.*

For specific guidance in making such a determination of fact, the court cited Example 9, of the guidelines 35-37 as an example of the reasoning the skilled artisan would apply in determining whether the skilled artisan was in possession of a genus of nucleic acids defined by their hybridization properties. *Enzo* 323 F.3d at 967, citing 66 Fed. Reg 1099 at 35-37. The court notes that, "such claims may be adequately described if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." *Id.* Finally, the Court concluded that if, on remand, the trial court finds that one of skill in the art would find the generically claimed sequences described on the basis of nucleic acid hybridization to an accessible structure consistent with the PTO Guidelines, then the written description requirement would be met. *Enzo* 323 F.3d at 968

B. Analysis of the Guidelines

Since the Federal Circuit in Enzo has adopted the standards for compliance with the written description requirement set forth the Guidelines, a review of two pertinent and properly described Examples in the Guidelines is warranted. In both exemplary cases, the claimed genuses are far larger and contain substantially less structural information than the genuses of claims 6 and 17 in the instant application.

Critical here is the understanding that in the art of molecular biology, structure and function are inextricably interrelated and that any definition of a biological macromolecule has

inherent functional and structural characteristics. The structure of a biomolecule has a direct bearing on its function. Conversely, given a particular function, often times the skill artisan might envisage a particular amino acid or nucleic acid structure necessary to carry it out.

The reader will note that the analysis of the claims of Examples 9 and 16, as well as the claims at issue, for compliance with the written description requirement, comprise two components, i.e. prongs, that inherently have both structural and functional aspects.

B.1. Proper description of a genus of antibodies in Example 16

The court in *Enzo* noted that the PTO would find compliance with § 112, ¶ 1, for a sample claim to an, "isolated antibody capable of binding to antigen X," given the disclosure of an isolated HIV antigen X. *Enzo* 323 F.3d at 964 citing the Written Description Guidelines, at 60.[2]

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[2]**Example 16: Antibodies**

Specification: The specification teaches that antigen X has been isolated and is useful for detection of HIV infections. The specification teaches antigen X as purified by gel filtration and provides characterization of the antigen as having a molecular weight of 55 KD. The specification also provides a clear protocol by which antigen X was isolated. The specification contemplates, but does not teach in an example, antibodies that specifically bind to antigen X and asserts that these antibodies can be used in immunoassays to detect HIV. The general knowledge in the art is such that antibodies are structurally well characterized. It is well known that all mammals produce antibodies and they exist in five isotypes, IgM, IgG, IgD, IgA and IgE. Antibodies contain an effector portion which is the constant region and a variable region that contains the antigen binding sites in the form of complementarity determining regions and the framework regions. The sequences of constant regions as well as the variable regions subgroups (framework regions) from a variety of species are known and published in the art. It is also well known that antibodies can be made against virtually any protein.

Claim: An isolated antibody capable of binding to antigen X.

The sample claim has two defining components "antibody" and "capable of binding antigen X." To understand the conclusion that the claim is properly described, both components must be analyzed together in view of one another. Independently, each component would not provide one of skill in the art with enough information to be convinced that the inventor was in possession the claimed genus. This is because the first component relates to all antibodies and the second component relates to all proteins capable of binding antigen X. As such, each of these components comprises a genus that encompass vast numbers of species with wildly divergent structures.

B.1.a. The structural component with functional aspects

The first component, "antibody," limits the universe of polypeptides because, as the court points out, "the well defined structural characteristics for the five classes of antibody, the [general] functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." *Id.* citing the Guidelines.[3] One of skill in the art would not then, expect much structural variation in the polypeptides covered by the term "antibody." As such, this term serves to limit the universe of polypeptides to those known as antibodies.

However, the genus of polypeptides encompassed by the term "antibody" may be quite large. The skilled artisan instantly appreciates that vast numbers of structurally similar antibodies will not fulfill the relevant function, i.e. binding antigen X. As such "antibody" is a mostly structural characterization with the only functional aspects relating to generalized and non-antigen X-specific properties of antibody binding.

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[3] In this context, the clause, "the functional characteristics of antibody binding," is not related to the relevant function of binding antigen X, rather it relates to binding of any antibody to any antigen.

B.1.b. The functional component with structural aspects

The second component, "capable of binding antigen X," is a mostly functional characterization with only vague structural aspects. For example, there may exist many different antibodies specific to dozens of different epitopes on antigen X. Moreover, the skilled artisan readily appreciates that a wide range of proteins might be capable of binding antigen X. Biology is replete with examples of proteins binding a wide range of other structurally unrelated proteins. For instance, antigen X could be bound by an endogenous homotypic or heterotypic binding partner, or it might bind a random assortment of polypeptides, all having an amino acid primary structure wildly divergent from that of the claimed antibody.[4] As such, "capable of binding antigen X" is a mostly functional characterization, but with structural aspects, in that the structure of such antibody also dictates whether it is "capable of binding antigen X."

Thus each component viewed separately delineates an extremely large and structurally diverse genus. Notwithstanding the vague generalized non-antigen X-specific functional information of the first component and the vague structural information gleaned from the second, the court, Guidelines and skilled artisan would be satisfied that the written description requirement is met upon reading the two claim components as complementing each other in terms of structure and function. Considering both the structural and functional components in combination, one of skill in the art would reasonably discount the inherent variability in either

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[4]In example 16, antigen X is purified from HIV and has a size of 55kd. Taking an example from basic biology of an antigen with a structurally diverse binding partners, let us consider that the α-chain component of the MHC class II were antigen X. The α-chain comprises a 30kd polypeptide chain. These proteins bind heterotypically to a complementary β-chain protein. Moreover, the α-chain binds an almost infinite variety of foreign and self polypeptides that are presented to circulating T-cells. This broad range of binding partners would not provide much structural information relating to recitation "capable of binding α-chain component of the MHC class II." Similarly, based on the model specification of Example 16, the skilled artisan would not necessarily glean very much structural information when envisaging any protein "capable of binding antigen X," and such a recitation encompasses a vast number of polypeptides.

component alone. As such, the claimed invention recites a "clear correlation between that function and a structure that is sufficiently known or disclosed." *Enzo* 323 F.3d at 968.

Furthermore, the Guidelines specifically recognize the intricacies of claiming biological macromolecules and suggest that they must be described by, "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, **or some combination of such characteristics**." *Enzo* 323 F.d at 964 citing the Guidelines, 66 Fed. Reg. at 1106 (emphasis added). It is the final phrase "or some combination of such characteristics," which is emphasized in Example 16, because the claim at issue covers a combination of interrelated structural and functional characteristics that are well known in the art and disclosed in the Example. Example 9, discussed below, relating to hybridization of nucleic acids contains a similar "combination."

B.2. Proper description of a genus of nucleic acids in Example 9

With respect to generically claimed nucleic acids, the court indicates that one of skill in the art will find generically claimed sequences defined on the basis of their hybridization to a known sequence, i.e. accessible structure, adequately described if they are consistent with Example 9 of the Guidelines. *Enzo* 323 F.3d at 968. Similarly to Example 16, Example 9 requires: 1) that a genus be defined such that the skilled artisan would not expect much structural variation within the genus and 2) that genus be limited by a required function related to the structure of the specific member of the genus.[5] Example 9 concludes that with respect to its

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[5]Example 9 contains the following hypothetical case:

Specification: The specification discloses a single cDNA (SEQ ID NO:1) which encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity. The specification includes an example wherein the complement of SEQ ID NO: 1 was used under highly stringent hybridization conditions (6XSSC and 65 degrees Celsius) for the isolation

exemplary claim:

> [A] person of skill in the art **would not expect substantial variation** among species encompassed within the scope of the claims [sic] because highly stringent conditions set forth in the claim yield structurally similar DNAs. Thus, a representative number of species is disclosed, **since highly stringent hybridization conditions *in combination* with the coding function of DNA** and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention. [emphasis added]

Guidelines at 35-37. Thus, it appears that the Guidelines reveal that the written description requirement would be met by claims reciting high stringent hybridization conditions in combination with a functional requirement where there is a relationship between structure and the relevant function.

B.2.a. Prong 1: The genus is defined such that the skilled artisan would not expect much variation within the genus

Applying the first prong of the analysis to Example 9, one of skill in the art **would not expect substantial variation** among species of nucleic acids encompassed within the scope of a generic claim reciting a genus of nucleic acids that is defined on the basis of hybridizing to a known DNA structure under highly stringent conditions. It is clear to even the most novice molecular biologist that such hybridization takes place only between very structurally similar

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> of nucleic acids that encode proteins that bind to dopamine receptor and stimulate adenylate cyclase activity. The hybridizing nucleic acids were not sequenced. They were expressed and several were shown to encode proteins that bind to a dopamine receptor and stimulate adenylate cyclase activity. These sequences may or may not be the same as SEQ ID NO: 1.
>
> **Claim:** An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO: 1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity.

DNA molecules. There will of course exist nucleic acids that hybridize under highly stringent conditions to the complement of the claimed reference SEQ ID NO: 1, but are not capable of the claimed exemplary coding function. However, the point of the first prong is to provide the skilled artisan with a reasonable genus within which they would not expect substantial structural variation. Therefore, this is a structural limitation with functional hybridization aspects. Thus, Example 9 mirrors Example 16, wherein in the range of proteins that can bind antigen X is structurally limited to antibodies.

B.2.b. Prong 2: The genus is limited by a required relevant function related to the structure of the specific member of the genus.

In the second prong, **the coding function of DNA** limits the universe of nucleic acids by requiring a function related to the structure of the that nucleic acid. Applicant asserts that in a similar manner to Example 16, where the limitation "binding antigen X" conveys only vague structural information, the limitation "nucleic acid . . . wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity," also provides insufficient structural information to distinguish the nucleic acid from others having the same functional ability. Standing alone, a functional DNA coding limitation does not necessarily include useful structural information because there might exist a multitude of potentially wildly unrelated nucleic acids sequences that can encode divergent polypeptides having the recited function above.

An analysis of Example 9 illuminates this concept. Dopamine receptors are part of a class of G protein-coupled receptors (GPCRs) that upon activation by receptor agonists activate an intracellular G-protein which then causes an increase in cyclic AMP by stimulation of adenylate cyclase.[6] Strictly speaking, one of skill in the art would realize that a protein that

[6]G protein-coupled receptors (GPCRs) are transmembrane spanning receptors. Most G protein-coupled receptors are intracellularly coupled to heterotrimeric G proteins. The agonist

"binds to a dopamine receptor and stimulates adenylate cyclase activity," could either be a G-protein coupled to the GPCR or an agonist protein, antibody or peptide that binds and activates the GPCR. For example, agonist auto-antibodies against GPCRs are known to be present and responsible for various disorders including those effected by GPCR-mediated neurotransmission.[7] Moreover, recent advances in antibody technology affords investigators the ability to make antibody-based receptor agonists to such receptors.[8] Additionally, the skilled artisan instantly recognizes that any potential structural DNA information contained in the "coding function of DNA" is obscured by the degeneracy in the genetic code which dictates that there are a vast number of nucleic acid molecules that can encode the same protein. Therefore, one would expect that the nucleic acids encoding such structurally divergent proteins as G-proteins, antibodies and single-chain antibody fragments, are substantially divergent from sample SEQ ID NO:1.

As such, the skilled artisan will realize that the functional limitation that a nucleic acid, "encode a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity," can only contain useful structural information **when viewed in combination** with the claim recitation requiring the same nucleic acid "specifically hybridize under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO: 1." Accordingly, in order for one of skill in the art to determine that an inventor was in possession of a given claimed

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activation of GPCRs stimulates G protein's dissociation of its α- and βγ-subunits. Once dissociated both the α- and βγ–subunits are free to modulate the activity of intracellular effector enzymes, e.g. adenylyl cyclase.

[7]For a review see Whitney et al., Annu Rev Neurosci. 1999; 22:175-95, discussing the study of diseases targeting molecules that regulate synaptic transmission at the neuromuscular junction and in the central nervous system, particularly diseases where autoimmunity produces agonist antibodies acting at two distinct G-protein-coupled receptors.

[8]Ledbetter et al., Crit Rev Immunol. 1997;17(5-6):427-35; discussing the agonistic activity of a CD40-specific single-chain Fv constructed from the variable regions of the monoclonal antibody G28-5.

genus of nucleic acids in the context of Example 9, he would require: 1) that the genus be defined such that the skilled artisan would not expect much variation within the genus (see Prong 1; B.2.a., supra) **and** 2) that the genus be limited by a required relevant function related to the structure of the specific member of the genus. Given the discussion supra, the skilled artisan realizes that because both prongs usually rest upon one another, often times both are necessary but not independently sufficient to have an adequately described claim.

Therefore, the sample claim in Example 9 represents a combination of interrelated structural and functional characteristics that are well known in the art and disclosed in the Example. As such it is properly described. According to *Enzo*, biomolecules must be described by, "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, **or some combination of such characteristics**." *Enzo* 323 F.d at 964 citing the Guidelines, 66 Fed. Reg. at 1106 (emphasis added).

C. Claims 6-11, 17-22 and 26 meet the requirements of 35 U.S.C. §112, first paragraph - Written Description

Applicant submits that one of skill in the art would know that the inventor was in possession of the claimed genuses of oligonucleotides in the context of Example 9, because: (Prong 1) the genus is defined such that the skilled artisan would expect so little variation within the genus, that the they would be convinced Applicant was in possession the claimed genuses. Alternatively, even if they were not convinced by Prong 1 alone, **the combination** of Prong 1 **and** Prong 2 and the that fact that the genuses are limited by a required function related to the structure of the specific member of a particular genus; would clearly convince them that the claims at issue are properly described in the instant specification.

Right off the bat, the skilled artisan would realize that the inherent interrelatedness of prongs 1 and 2 represents "relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with

a known or disclosed correlation between function and structure, **or some combination of such characteristics.**" *Enzo* at 323 F.3d at 964 citing the Guidelines, 66 Fed. Reg. at 1106 (emphasis added).

The claims at issue recite a genus of purified oligonucleotides consisting of a particular reference sequence (i.e., SEQ ID NOs: 1, 2, 7 or 8), or sequences which are at least 80% identical therewith and hybridize to a complement of their reference sequence under stringent conditions; wherein the isolated and purified oligonucleotide is capable of amplifying a particular portion of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with a specifically recited second oligonucleotide (SEQ ID NO: 2, 1, 7 or 8, respectively). Claim 6 requires that a the claimed oligonucleotides be capable of amplifying a portion of the 5' untranslated region and Exon 1 of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 2 or 1, respectively. Claim 17 also requires that the claimed oligonucleotides be capable of amplifying a portion of Exon 6 of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with a SEQ ID NO: 8 or 7, respectively.

C. 1. Prong 1: The genus is defined such that the skilled artisan would not expect much variation within the genus

As stated in the Guidelines, a claim element requiring members of the genus to hybridize to a complement of a given reference sequence under stringent conditions provides the skilled artisan with a genus within which they **would not expect substantial structural variation** among species of oligonucleotides. The "stringent conditions" recited in the claims at issue are defined in the specification as what one in the art would consider "highly stringent" in the

context of Example 9 of the Guidelines.[9] As stated *supra*, it is clear to even the most novice molecular biologist that such hybridization takes place only between very structurally similar DNA molecules. Additionally, the skilled artisan would expect far less structural variation among the claimed oligonucleotides given the claimed genuses' requirement for hybridization to a reference sequence; than among all antibodies with the genus "antibody" delimited from the universe of polypeptides as described in Example 16, (see B.2.a.; *supra*).

This proposition is directly supported in the instant application specification. With respect to stringent hybridization to a model reference oligonucleotide, the specification teaches on page 10, paragraph 23, that such conditions would prevent hybridization of nucleic acids of having more than 4 or more mismatches out of 20 contiguous nucleotides, more preferably 2 or more mismatches out of 20 contiguous nucleotides and most preferably 1 or more mismatches out of 20 contiguous nucleotides. Moreover, further structural information may be gleaned from page 10, paragraph 24, which indicates that the minimum length for the hybridizing portion of the oligonucleotide to the reference oligonucleotide is at least 10, for example 15, nucleotides in length. The skilled artisan would not consider such a genus of oligonucleotides hybridizing to the model 20-mer to have substantial variation, regardless of the ultimate size of the genus.

Claim 6 requires that its claimed oligonucleotides hybridize to a complement of reference sequence SEQ ID NO: 1 (19 bases in length) or to a complement of reference sequence SEQ ID NO: 2 (20 bases in length) under stringent conditions. Claim 17 requires that its claimed

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[9]The specification teaches the parameters for hybridization of an oligonucleotide primer to a nucleic acid sample under stringent conditions such that one of skill in the art would consider them to be "highly stringent" within the context of Example 9 of the Guidelines. See paragraphs 25-26, pp.10-11. The specification teaches exemplary stringent conditions to involve hybridizing in 5x SSC/5x Denhart's solution/1.0% SDS, and washing conditions from about 0.2x SSC/0.1% SDS to about 3x SSC. For example, in order to hybridize a test oligonucleotide to SEQ ID NO: 1 (T_m, = 59^{0}C) under the specification's "stringent" conditions, one might select a washing temperature of about 39^{0}C. Example 9 of the Guidelines discloses "highly stringent" hybridization conditions of 6XSSC and 65 degrees Celsius but provides no washing conditions.

oligonucleotides hybridize to a complement of reference sequence SEQ ID NO: 7 (23 bases in length) or a complement of reference sequence SEQ ID NO: 8 (21 bases in length) under stringent conditions. Moreover, the claims further structurally define the claimed genuses in requiring that all oligonucleotides to be at least 80% identical to their reference sequence.

The skilled artisan could not expect substantial variation in structure of the claimed oligonucleotides because the hybridization of two nucleic acids hybridize under stringent conditions to one another, directly depends on the proportion and order of complementary nucleotides shared between them over their length. Given a reference sequence on the order of approximately 20 nucleotides, they would have a solid description of the structure of oligonucleotides that would hybridize to it under stringent conditions. As such, the claimed hybridization conditions are considered in the Guidelines and by the PTO to be a structural limitation with strong functional aspects.

However, as with Example 9, although one of skill in the art would not expect substantial variation within the claimed genuses, there will of course exist nucleic acids that will specifically hybridize under highly stringent conditions to the complement of the reference sequence in a manner set forth the specification, yet will not have the capability to amplify a portion of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with a specifically recited second oligonucleotide. In Example 9, there existed nucleic acids that although hybridizing to exemplary SEQ ID NO: 1, will not have the claimed coding function. This was also the situation in the analysis of Example 16 in which it was clear that there exist antibodies that although structurally similar, will not bind antigen X. However, the skilled artisan recognizes that given the disclosure of the reference sequences and the fact that oligonucleotides only hybridize structurally similar sequences, there is substantial structural description for the claimed genuses with respect to hybridization conditions alone.[10]

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[10]The court pointed out that because of the, "well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the

Alternatively, in *Eli Lilly*, the '525 patent did not disclose the structure, i.e. sequence, of any reference nucleic acid encoding human or rat insulin. Moreover, the '525 patent merely disclosed a method of isolating a human insulin cDNA based on molecular size and not nucleic acid identity. This is the reason why, when assessing claims to human cDNA, the court concluded that an adequate written description of genetic material "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly* at 1566, 43 USPQ2d at 1404 (quoting *Fiers v. Revel*, 984 F.2d at 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993)). *Eli Lilly* does not apply to the claims at issue. The skilled molecular biologist would not consider the hybridization conditions in combination with the disclosed reference sequences (SEQ ID NO: 1, 2, 7 & 8) to constitute a mere "mere wish or plan for obtaining the claimed chemical invention." *Id.* Rather, they would consider them to be a structurally precise characterization comprising, a reference structure and physical properties.

Based on the description of the reference sequences (SEQ ID Nos: 1, 2, 7 & 8), hybridization conditions as set forth in the specification, and the requirement that the claimed oligonucleotides are at least 80% identical to their reference sequences, the skilled artisan would believe that the Applicant was in possession of the claimed oligonucleotides.

However, even if the skilled artisan were not satisfied that the Applicant had adequately described oligonucleotides hybridizing under stringent conditions to the reference sequences SEQ ID Nos: 1, 2, 7 & 8, they would certainly be convinced upon viewing a such claim elements (i.e. Prong 1; C.1., *supra*) **in combination** with functional limitations with the strong structural

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antibody technology is well developed and mature." *Enzo* at 323 F.3d at 964. As stated supra in the section analyzing Example 16, in this context, the clause, "the functional characteristics of antibody binding," is not related to the relevant function of binding antigen X, rather binding of any antibody to any antigen. Similarly here, oligonucleotides are well known in the art as a short stretch of nucleotides often used as a probe or primer to hybridize to a target sequence. The factors dictating such generalized oligonucleotide "binding" are at least as well understood as antigen-antibody interactions.

attributes discussed below (Prong 2; C.2., *infra*).

C. 2. Prong 2: The genus is limited by a required function related to the structure of the specific member of the genus

In addition to the hybridization and at least 80% identity structural requirements, the claims at issue further contain functional limitations directly relating to the claimed oligonucleotides' structure. The claims at issue require that the claimed oligonucleotides are capable of amplifying a portion of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with a specifically recited second sequence, respectively. Claim 6 further requires that the claimed oligonucleotides are capable of amplifying a portion of the 5' untranslated region and Exon 1 of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with a SEQ ID NO: 2 & 1, respectively. Claim 17 further requires that a the claimed oligonucleotides be capable of amplifying a portion of Exon 6 of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with a SEQ ID NO: 8 & 7, respectively.

Whereas, the second prong of the analysis of Example 9 (B.2.b.; *supra*), rests on the "coding function of DNA," in the claims at issue the **amplification** function of DNA limits the universe of oligonucleotides by a requiring a function related to the structure of the oligonucleotide.

The skilled artisan will appreciate that the nucleic acid structural information conveyed by a functional limitation involving amplification is substantially more specific than that involving coding. First, one will instantly realizes that any variation in the claimed genuses as defined by the hybridization conditions, will not be compounded by degeneracy of the genetic code because there is no "coding function of DNA" involved in this context and as such, it cannot expand the structural limits of claimed genus.

Furthermore, one will glean many structural facts from the "amplification function" as

recited, without even considering the identity of the reference sequence. This is not the case in either Example 16 or 9 of the Guidelines. For instance in Example 16, the limitation, "binding antigen X," conveys only vague structural information. Furthermore, in Example 9 the limitation "nucleic acid . . . wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity," does not provide sufficient structural information to distinguish the nucleic acid from others. Examples 16 and 9 both comprise a vast number of wildy structurally divergent polypeptides and nucleic acids, respectively, capable of the exemplary claimed functions.

Conversly, there is more information regarding the structure of an oligonucleotide whose function is to amplify a portion of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with a specifically recited second sequence. First, the *DPD* cDNA sequence is known. One of skill in the art knows that in order to fulfill its amplification function, each potential primer oligonucleotide (species within the claimed genuses) must very closely complement the known sequence of the template DNA to be primed for amplification. Second, due to the fact that the template to be amplified, is derived from fixed and paraffin embedded (FPE) tissue, one of skill in the art knows that regardless of template identity, template fragments will be no more than 100-200 bases in length. Therefore, given a specifically recited second sequence with which to complete a primer pair, the skill artisan realizes that the claimed oligonucleotide can only be located 100-200 bases away.

The skilled artisan also has a basic skill set with respect to selecting oligonucleotide primers for DNA Polymerase Chain Reaction (PCR) amplification. For example, one would dismiss oligonucleotides that are shorter than 9 bases because they will not function in PCR amplification due to the minimum contact surface between Taq polymerase with the double-stranded DNA template (Williams *et al.*, Nucleic Acids Res. 1990 Nov 25; 18 (22): 6531-5). They also know that in order to function as an effective PCR primer, an oligonucleotide should preferentially have as close to a 50:50 G:C ratio as possible.

However, the skilled artisan would also take into account that the sequence of any given useful oligonucleotide primer can easily be altered with respect to a very small number of nucleotides and still retain amplification function. For example, provided with a known DNA template (e.g. *DPD* cDNA sequence) and an effective primer reference oligonucleotide (e.g. SEQ ID NO: 1); the skilled artisan would realize that the SEQ ID NO: 1 could be modified simply by moving it forward or backward along the template by a small number of bases. This can easily be accomplished by deleting nucleotides from one end and adding the same number of nucleotide bases to the other. The identity of the added bases is dictated by the sequence of the template DNA. Moreover, the skilled artisan realizes that SEQ ID NO: 1 could be shortened by simply deleting a very small number of bases or it could be lengthened by adding a very small number of bases as dictated by the template and still have an oligonucleotide that maintains its functionality as an effective PCR primer. Finally, they also know that an SEQ ID NO: 1 could be modified by substitution of a very small number of bases and still have an oligonucleotide that maintains its functionality as an effective PCR primer.

Taking into account what one of skill knows regarding primer design in the this context, the functional limitations at issue here, i.e. "an oligonucleotide . . . wherein said isolated and purified oligonucleotide is capable of amplifying a portion of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with," SEQ ID NO: 1, 2, 7 or 8, respectively, provides substantially more structural information than the functional limitations in Examples 9 and 16 of the Guidelines. Moreover, the structural facets of this functional description become greater still were the claim to define the subsection of the template DNA to be amplified. The claims at issue provide a reference sequence (e.g. SEQ ID Nos: 1, 2, 7 & 8) as well as a template DNA sequence to be amplified (that corresponding to *DPD* mRNA). Additionally, claim 6 requires that the portion of the template to be amplified corresponds to the 5' untranslated region (UTR) and Exon 1 of the *DPD* mRNA. Claim 17 requires that the portion of the template to be amplified corresponds to Exon 6 of the *DPD* mRNA. The skilled artisan readily knows how to identify and read these template

sequences.

Accordingly, one of skill in the art would be satisfied that Applicant was in possession of a given claimed genuses of oligonucleotides at issue because: 1) that the genuses have been defined such that the skilled artisan would not expect much variation within each genus (Prong 1; C.1.) **and** 2) that genuses are limited by a required function related to the structure of the specific member of the genus. As indicated above and adopted by the court in *Enzo*; the Guidelines conclude that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, **or some combination of such characteristics."** *Enzo* 323 F.3d at 964 citing the Guidelines, 66 Fed. Reg. at 1106 (emphasis added). The skilled artisan realizes that because these prongs complement one another in terms of structure and function and that the functional amplification limitation provides substantial structural information, the prongs constitute **a combination** of physical properties, functional characteristics that are coupled with a known or disclosed correlation between function and structure, and that as such, they are sufficient to properly describe the claimed genuses.

D. Response to Examiner's Arguments:

D.1. The Examiner is misapplying the facts and law of *Eli Lilly*

The Examiner rejects the claims 6-11, 17-22 and 26 under 35 U.S.C. § 112, first paragraph, as allegedly encompassing subject matter lacking sufficient written description. The Examiner asserts that because the specification discloses four distinct oligonucleotide primer reference sequences (SEQ ID NOs: 1 and 2 and SEQ ID NOs: 7 and 8), the specification does not describe sequences that are are at least 80% identical therewith, respectively, and that hybridize to the complement of their reference sequence under stringent conditions; wherein the isolated

and purified oligonucleotides are also capable of amplifying a particular portion of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with a specifically recited second oligonucleotide (SEQ ID NO: 2, 1, 8 or 7, respectively).

The gist of the Examiner's argument is that the claims at issue do not have sufficient structural description in the specification. As support for his assertion the Examiner argues that

> [I]n [*U.C. v. Eli Lilly*] there was also structure, the prior art rat insulin protein, which shared 80% homology with the human insulin sequence. However, in Lilly, this 80% homology was found to be insufficient to support the claim to the human insulin sequence. Consequently, in the current case, where the 80% homology is tied solely to functional elements which are inherent in the sequences, the claims remain insufficiently described.

See Final Office Action mailed February 2, 2003. The Examiner is plainly misapplying not only the facts but also the legal holding of *Eli Lilly*. First, the Examiner is somehow equating the alleged 80% homology between human and rat insulin **protein** in *Eli Lilly* with the claim recitation that the claimed oligonucleotides, which are **nucleic acids**, have at least 80% **identity** with their reference SEQ ID NO:1, 2, 7 or 8. Even if the rat and human insulin proteins were 80% homologous as the Examiner asserts, taking into account conservative amino acid variances, protein-protein alignment, and degeneracy of the genetic code, the identity of nucleic acids encoding each protein would be far less than 80%. The skilled artisan therefore appreciates that **homology in the context of amino acid sequences** and **strict nucleotide identity in the context of nucleic acids** are proverbial "apples and oranges" and as such, cannot be logically compared.

Moreover, the Examiner suggests that the insufficient homology between rat and human insulin proteins was the reason that the claims in that case were held invalid. This is simply incorrect. The reason the claims to human cDNA were held invalid in *Eli Lilly*, were not because of insufficient homology between human and rat insulin protein, or even insufficient identity

between a rat and human insulin cDNA, but because although the human insulin protein sequence was disclosed, there was **no disclosure of any rat or human cDNA sequence** encoding the human insulin protein.

In *Eli Lilly*, the court held that genetic material that has only been defined by a statement of function or result is not adequately described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. In *Eli Lilly*, the court further determined that a claim to a microorganism containing a human insulin cDNA was not adequately described by a statement that the invention included human insulin cDNA. *Id.* at 1567, 43 USPQ2d at 1405. The court stated, "DNA is not itself a written description of that cDNA; it conveys no distinguishing information concerning its identity." Because there was no disclosure of **any** cDNA encoding the any insulin protein, the functional result of encoding the human insulin protein was not sufficient on its own. The court concluded that there was no "precise definition, such as by structure, formula, chemical name, or physical properties," with respect to the recitation "human cDNA," and therefore, that the claim to a human insulin cDNA embodied, "a mere wish or plan for obtaining the claimed chemical invention." *Id.* at 1566, 43 USPQ2d at 1404 (quoting *Fiers v. Revel*, 984 F.2d at 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993)).

D.2. The Examiner is incorrect in asserting that the claims recite "solely functional elements"

Applying Example 9 of the Guidelines to the situation in *Eli Lilly*, the disclosure of a **single** human insulin coding cDNA, as well as highly stringent hybridization conditions, **would have** provided sufficient written description for **all nucleic acids that hybridize under highly stringent conditions** to that cDNA (see Prong 1; B.2.a., *supra*) and **encode human insulin** (see Prong 2; see B.2.b., *supra*). The missing structural information in Eli Lilly's recitation, "cDNA," are supplied by a requirement for hybridization to a disclosed single human insulin cDNA under highly stringent conditions. Again, under such conditions the skilled artisan would not expect

substantial structural variation among nucleic acids hybridizing to a hypothetically disclosed single human insulin cDNA.

By extension, the Examiner's erroneous conclusion that any similarity between oligonucleotides within the instant claimed genuses, "is tied solely to functional elements which are inherent in the sequences," is not consistent with *Eli Lilly*, *Enzo*, or the Guidelines. The claims at issue in the subject application all recite a reference oligonucleotide (SEQ ID NO:1, 2, 7, & 8), and relate to oligonucleotides that hybridize under stringent conditions to their respective reference sequences. Given the fact that the reference oligonucleotides range from 19-23 nucleotides in length, one of skill in the art would expect substantially less variation then if they had the length of an average open reading frame (ORF) generally containing hundreds of nucleotide bases encoding a polypeptide having dozens of amino acids. Again, variation within the claimed genuses is also limited by the fact that degeneracy of the genetic code does not come into play. Additionally, the claimed oligonucleotides must also be at least 80% identical to their reference sequences thereby further limiting the genus to a finite number of oligonucleotides.

Applicant submits that the claimed limitations for stringent hybridization and at least 80% identity to given reference sequence are sufficiently described in the instant specification to show possession of the claimed oligonucleotides. However, even if it were not, one of skill in the art would find sufficient description when assessing the requirements for hybridization and at least 80% identity to the reference sequences **in combination** with the claimed oligonucleotides' amplification function.

D.3. The Examiner makes erroneous assumptions about the molecular biology of PCR

The Examiner indicates that he is not satisfied with subject specification's structural description of the claimed oligonucleotides and demands to be shown which changes could be made to the reference SEQ ID Nos: with respect to which "motifs which need to be conserved." One of skill in the art of molecular biology and familiar with the design of PCR primers readily

appreciates that beyond a set number of specific parameters such as template sequence, melting temperature and GC content, it is nearly impossible to predict whether a specific primer will work until tried. Additionally, one would also know that PCR primers are generally not described in terms of conserved "motifs." As such, demanding that the inventor disclose "motifs" in the context of 20-mer PCR primers amounts to an unreasonable burden in order to obtain fair patent coverage on novel primers.

Next, the Examiner erroneously concludes that there is no structural information whatsoever, in the claims' recitation that "an oligonucleotide . . . wherein said isolated and purified oligonucleotide is capable of amplifying a portion of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with," either SEQ ID NO: 1, 2, 7 or 8, respectively. The Examiner indicates that such a limitation, "is available to any sequence whatever."

The Examiner supports this factually tenuous position by further opining that, "any sequence mixed with exon 1 of *DPD* would be capable of amplifying that sequence to some extent." The Examiner gives no reasoning as to why he feels that, "any sequence mixed with exon 1 of DPD" could amplify it. This is simply not true and one of skill in the art could not argue otherwise.

One of skill in the art would not believe that "any" sequence simply "mixed" with exon 1 of the DPD cDNA could yield an amplified *DPD* sequence. It is elementary that the primers must be complex enough so that the likelihood of annealing to sequences other than the chosen target template DNA is very low. Accordingly, only specific sequences will amplify specific template DNA and, as such, design of appropriate primers is an area of intense commercial interest. Moreover, GC content and melting temperatures are critical factors in designing primers for PCR.

For additional support, the Examiner argues that "random hexamers are frequently used for such amplifications." Applicant protests that the realities of basic molecular biology are not being taken into account. This statement is seriously misguided on several levels. First, the

skilled artisan would never use a hexamer, random or template specific, of any sort in PCR because they are too short (required minimum is 9 bases) and will not function in PCR amplification due to the minimum contact surface between Taq polymerase with the double-stranded DNA template (Williams et al, Nucleic Acids Res. 1990 Nov 25; 18 (22): 6531-5). Secondly, the skilled artisan might use random hexamers to synthesize the first strand of cDNA from mRNA using the viral enzyme reverse transcriptase. This, however, cannot be characterized as amplification. PCR amplification is performed on the cDNA itself using the type of specific oligonucleotides presently claimed. It is clear that if one were to not understand PCR, one would also not understand how the function of amplifying a particular region of DNA would impart very specific structural information about the primers used.

D.4. The Examiner mistakenly concludes that the coding function of DNA in Example 9 provides more structural information than the claimed amplification function

In an Office Action mailed July 11, 2003 in related application U.S. Ser. No. 09/842,111, filed April 26, 2001, our docket 11220/128, regarding the same issue, the Examiner opines that the "coding function of DNA," as exemplified in Example 9 of the Guidelines, contains more structural information than the amplification function of the claimed oligonucleotides because, "this is a very specific function for the protein which strongly delimits nucleic acids."(page 5, line 10). The Examiner asserts that the coding function of Example 9 requires that the, "nucleic acid must encode the protein, therefore indicating that no stop codons were permitted, the protein must retain binding ability, meaning that very [sic] the binding domain must be unaffected and must activate adenyl [sic] cyclase, which is drawn to the activation domain of the protein." (Page 5, lines 15-19)

However, the analysis of Example 9 in B.2.b. and in C.2., *supra*, plainly shows that the "coding function of DNA" in fact, **does not** strongly delimit nucleic acids, *per se*. Again, many proteins of different and unknown structure could have the ability to bind the dopamine receptor

and activate andenylate cyclase. Accordingly, one of skill in the art would realize that the protein to be encoded in Example 9 could, among others, be a G-protein coupled to the GPCR, an agonist pepetide or agonist antibody/antibody fragment that binds GPCR extracellularly or intracellularly. Any of these could modulate the activation of adenylate cyclase. Additionally, the degeneracy in the genetic code will compound the structural variation by geometrically increasing the number of nucleic acids in the genus of the model claim in Example 9. Taken together, one would expect that the nucleic acids encoding structurally divergent proteins will be substantially divergent from the Example 9's SEQ ID NO:1. Therefore, the example provides only useful structural information when the coding function is viewed in light of SEQ ID NO: 1. The Examiner is unwittingly assessing the structural information of the "coding function of DNA" (Prong 2; B.2.b., *supra*) in Example 9, **in combination with** the sample reference sequence SEQ ID NO:1 and those nucleic acids that hybridize to it under stringent conditions (Prong 1; B.2.a., *supra*).

However, the Examiner is inconsistent in his examination of the claims at issue. In the instant application, **the Examiner refuses** to view the amplification function of the claimed oligonuclotides (Prong 2; C.2., *supra*) **in combination with** their disclosed reference sequences and the further structural limitation that the claimed oligonucleotides hybridize to their reference sequences under stringent conditions (Prong 1; C.1., *supra*) and also be at least 80% identical thereto. **In evaluating the claims at issue, the Examiner is not acting as one of skill in the art would**. In other words the Examiner is not viewing Prong 2 (C.2., supra) in combination with Prong 1 (C.1., supra) of the written description analysis in combination as he has done in his analysis of Example 9 from the Guidelines. Due to mistaken assumptions relating to PCR technology and molecular biology, this subtlety has not been appreciated.

A further example of this flawed logic combined with erroneous assumptions is evidenced in the Office Action mailed July 11, 2003 in the related application U.S. Ser. No. 09/842,111, regarding the same written description rejection applied to related claims. The

Examiner hypothesizes that his reading of the claims at issue, independantly include both an oligonucleotide that because of its 80% identity will inherently hybridize to the reference sequences (Prong 1; C.1., *supra*); and alternatively and independently a 2-mer that will function to amplify a portion of the *DPD* target. (Prong 2; C.2., *supra*). In viewing the claimed oligonucleotides' amplification function alone, the Examiner has apparently disregarded all of the information at the disposal of one of skill in the art regarding PCR primer design. Again, the skill artisan would never believe that a 2-mer, a random hexamer, or even a random 20-mer could amplify a specific target DNA strand.

However, when reading the amplification function (Prong 2, C.2., *supra*) together with the structural limitations of hybridization (Prong 1, C.1., *supra*) and 80% identity, the skilled artisan would clearly be convinced that Applicant had adequately described and was therefore in possession of the claimed oligonucleotides.

It is respectfully submitted that the specification adequately describes the claimed genuses of oligonucleotides such that claims 6-11, 17-22 and 26 meet the requirements of 35 U.S.C. § 112, first paragraph. For the reasons set forth above, Applicant respectfully requests that the rejection of these claims be withdrawn.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejects claims 6-11, 17-22 and 26 under 35 U.S.C. § 103 (a) as allegedly being unpatentably obvious over Gonzales et al., U.S. Patent No. 6,015,673 in view of Willhauck et al., Biotechniques, 1998, 25:656-659. The Examiner alleges that SEQ ID NO: 5 of Gonzales et al. teaches an oligonucleotide comprising 14 of claimed SEQ NO: 1's 19 nucleotides. The Examiner asserts that Gonzales' SEQ ID NO: 5 is 73% identical to the claimed oligonucleotide SEQ ID NO: 1. Morever, the Examiner asserts that Gonzales teaches the sequence of *DPD* cDNA and therefore anticipates all oligonucleotides necessary to amplify it. Applicants respectfully disagree. The Examiner further opines that the use of an internal control gene is taught by Willhauck.

Independent claim 6 requires the use of certain oligonucleotides to amplify a portion of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA. Specifically, claim 6 relates to subjecting *DPD* mRNA to amplification using a pair of oligonucleotide primers: SEQ ID: 1, or an oligonucleotide primer at least 80% identical therewith and hybridizes to a complement of SEQ ID NO: 1 under stringent conditions; wherein said isolated and purified oligonucleotide is capable of amplifying a portion of the 5' untranslated region and Exon 1 of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 2, **and** SEQ ID: 2 or an oligonucleotide primer at least 80% identical therewith and hybridizes to a complement of SEQ ID NO: 2 under stringent conditions; wherein said isolated and purified oligonucleotide is capable of amplifying a portion of the 5' untranslated region and Exon 1 of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 1; to obtain an amplified sample.

Alternatively, independent claim 17 requires the use of certain oligonucleotides to amplify a different portion of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA. Specifically, claim 17 relates to subjecting *DPD* mRNA to amplification using a pair of oligonucleotide primers: SEQ ID: 7, or an oligonucleotide primer at least 80% identical therewith and hybridizes to a complement of SEQ ID NO: 7 under stringent conditions; wherein said isolated and purified oligonucleotide is capable of amplifying a portion Exon 6 of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 8, **and** SEQ ID: 8 or an oligonucleotide primer at least 80% identical therewith and hybridizes to a complement of SEQ ID NO: 8 under stringent conditions; wherein said isolated and purified oligonucleotide is capable of amplifying a portion of Exon 6 of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 7; to obtain an amplified sample.

Applicant respectfully asserts that Gonzales does not teach a single oligonucleotide primer that is at least 80% identical to either SEQ ID NO: 1 or 2. Moreover, Gonzales does not

teach a single oligonucleotide that is that is at least 80% identical to SEQ ID NO: 7 or 8. Additionally, the Examiner has not brought to light any other teaching, suggesting or contemplation of an oligonucleotide primer that is at least 80% identical to SEQ ID NO: 1, 2, 7 or 8.

Most poignantly, however, even if any of the references did teach an oligonucleotide at least 80% identical to any of these oligonucleotides, there is nothing of record that teaches the use of **any combination of** these oligonucleotides together to amplify a portion of the a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA. Moreover, even if, as the Examiner alleges, Gonzales generically taught designing oligonucleotide primers from *DPD* cDNA, Applicant asserts that the Examiner has pointed to no motivation whatsoever as to why one of skill in the art would use the combination of oligonucleotides claimed in claim 6 or claim 17 to amplify a portion of a *Dihydropyrimidine Dehydrogenase (DPD)* mRNA.

Accordingly, it is the position of the Applicant that the shortcomings of Gonzales cannot be remedied by the alleged teaching in Willhauck of the use of an internal control gene.

In view of the remarks and amendments made herein, Applicant respectfully asserts that the rejection is traversed, and withdrawal thereof is respectfully requested.

CONCLUSION

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 11-0600.

Respectfully submitted,

KENYON & KENYON

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